Leukemia Following Low-Dose Total Body Irradiation and Chemotherapy for Non-Hodgkin's Lymphoma

By Lois B. Travis, Jane Weeks, Rochelle E. Curtis, John T. Chaffey, Marilyn Stovall, Peter M. Banks, and John D. Boice, Jr

Purpose: Low-dose total body irradiation (TBI) is used to treat non-Hodgkin's lymphoma (NHL) and several other malignancies. Large volumes of bone marrow and other tissue receive considerable exposure, but few studies have quantified late carcinogenic sequelae.

Patients and Methods: A cohort of 61 2-year survivors of NHL treated initially with low-dose TBI was monitored for second cancer occurrence. Data on primary and subsequent therapy were collected, and cumulative dose of radiation to active bone marrow (ABM) (median, 5.2 Gy) was reconstructed.

Results: Thirteen second primary cancers occurred. Four patients developed acute nonlymphocytic leukemia (ANLL), which represents a relative risk (RR) of 117 (95% confidence interval [CI], 31.5 to 300) compared with population rates. A fifth patient was diagnosed with myelodysplastic syndrome (MDS). All five patients with secondary hematologic malignancies subsequently received salvage treatment, with either alkylating agents alone (n = 1) or combined modality therapy (CMT) (n = 4). Overall, eight solid tumors were observed (RR = 2.0; 95% CI, 0.9 to 4.0). The 15-year cumulative risks of all second cancers and secondary ANLL were 37% and 17%, respectively.

Conclusions: Despite the small number of subjects, a considerable risk of leukemia was observed among patients treated with low-dose TBI in combination with CMT including alkylating agents. Based on these results, approximately eight to nine excess ANLLs might be expected to occur among 100 NHL patients treated with low-dose TBI and salvage treatment and followed-up for 15 years.

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ALTHOUGH most radiotherapy for malignant disease involves the delivery of large amounts of radiation to relatively small volumes of diseased tissue, some systemic cancers are treated with low-dose total body irradiation (TBI).[1,2] This treatment modality uses very low individual TBI fraction sizes (most commonly .1 to .15 Gy) given several times a week until a cumulative dose of approximately 1.5 Gy has been administered. Higher total doses of TBI (eg, 10 Gy) are used in preparatory regimens for bone marrow transplantation.[3] Renewed interest in low-dose TBI is seen in the management of non-Hodgkin's lymphoma (NHL),[4-7] chronic lymphocytic leukemia (CLL),[4,7,8] and certain nonneoplastic conditions.[9,10] However, there are few data on the long-term effects of therapeutic low-dose TBI,[5,11,12] despite its previous use[2,11,13-21] and the current interest in therapeutic applications.[4-10] Most recently, Mendenhall et al[12] noted the occurrence of secondary myeloproliferative disorders in four of 44 patients given TBI as primary treatment for NHL.[12] We report the 15-year follow-up data of a unique group of patients given low-dose TBI for NHL and compare risks of secondary leukemia with those seen in lymphoma patients initially treated with other modalities.

PATIENTS AND METHODS

Study Subjects

A retrospective follow-up study was conducted among all NHL patients treated initially with low-dose TBI at the Harvard Joint Center for Radiation Therapy (JCRT) in Boston, MA.[22] The present survey is part of a multicenter investigation, with results for institutions that did not routinely use low-dose TBI reported separately.[23] Eligibility criteria for all sites included a diagnosis of NHL as the first primary cancer from January 1, 1965 through December 31, 1980; age between 18 and 70 years at time of initial diagnosis; and survival of ≥ 2 years.[24] All 61 patients within the final JCRT cohort also received low-dose TBI as primary therapy for NHL, with a portion of these subjects included in an earlier survey.[16]

NHL patients were traced for vital status, occurrence of second primary cancers, and subsequent therapy through the end of the study (December 31, 1991). Sources of data included the JCRT, local hospitals and outpatient clinics, other radiotherapy facilities, and offices of private physicians. For all reported cases of secondary acute nonlymphocytic leukemia (ANLL) or myelodysplastic syndrome (MDS), clinical records and bone marrow pathology reports were reviewed to ensure that cases did not represent leukemic progressions of NHL. The five eligible cases included four patients with ANLL and one with MDS, according to the criteria of Bennett et al.[25,26] All cases are subsequently referred to as ANLL for simplicity of presentation.

Diagnoses of solid tumors were established through examination of pathology reports in seven of eight cases. In one subject, a diagnosis of breast cancer was accepted based on patient presentation, mammographic findings, and clinical assessment of the attending

From the Radiation Epidemiology Branch, National Cancer Institute, National Institutes of Health, United States Department of Health and Human Services, Bethesda, MD; Dana-Farber Cancer Institute; Harvard Joint Center for Radiotherapy, Boston, MA; University of Texas M.D. Anderson Cancer Center, Houston; and University of Texas Health Sciences Center, San Antonio, TX.

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Address reprint requests to Lois B. Travis, MD, National Cancer Institute, Executive Plaza North, Suite 408, Bethesda, MD 20892.

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physician. Initial diagnoses of NHL were confirmed by review of pathology reports, and classified into one of the major subgroups of the Working Formulation.[27]

Data Abstraction: Radiation and Cytotoxic Drug Exposure

Standardized abstract forms were used to collect demographic and medical record data, including information on all NHL treatment, using the sources listed earlier. TBI was administered using megavoltage equipment, with patients typically treated with a dose of 0.15 Gy twice a week until a cumulative dose of approximately 1.5 Gy was reached. Forty-six patients subsequently received local radiotherapy with fields located in the abdomen and/or pelvis (33%), chest and/or mantle (17%), abdomen and/or pelvis plus chest and/or mantle (41%), head and neck only (79%), or other (2%). Detailed radiotherapy records were used to estimate radiation dose to 17 partitions of active bone marrow (ABM)[28] for each treatment course. For patients given subsequent involved-field therapy, absorbed dose to ABM in a treated volume was calculated using standard radiotherapy depth dose data. Dose to ABM in areas outside radiation beams was calculated by measurement in water phantoms.[28] An overall mean ABM dose was derived by summing weighted doses to individual bone marrow partitions. Bone marrow doses were substantially greater from local radiotherapy (5 Gy) than TBI.

Salvage therapy that included alkylating agents was administered to 41 patients. The names of chemotherapy protocols and cytotoxic drugs and dates and duration of administration were abstracted from medical records.

Statistical Analysis

Person-years (PY) of observation were compiled according to age, sex, and calendar-year period from 2 years after date of NHL diagnosis to the date of last follow-up visit, date of diagnosis of ANLL or other second primary cancer, date of death, or end of study (December 31, 1991), whichever occurred first. Incidence rates from the Connecticut Tumor Registry specific for age, sex, and 5-year calendar-year periods were multiplied by the accumulated PY at risk to estimate the number of expected cancers. Statistical tests and 95% confidence limits were based on the assumption that cases followed a Poisson distribution. The cumulative relative probability of developing a secondary malignancy was calculated using Kaplan-Meier methods.[29]

The excess risk (excess number of cases of leukemia per 10,000 patients) within the first 15 years after diagnosis of NHL was estimated by subtraction of the expected number from the number observed; division of the difference by PY of follow-up and then multiplication by 13 (which is the number of years at risk, assuming a latent period of 2 years before the onset of leukemia) and by 10^4. For example, four observed cases of ANLL compared with 0.03 expected during 594 PY of follow-up evaluation would correspond to an estimated excess of approximately 869 ANLLs per 10,000 patients over 15 years: $(4 - 0.03)/594 \times 13 \times 10^4 = 869$. Diagnoses of MDS were not included in calculations of observed-to-expected ratios (0/E) or excess risk, since underlying incidence rates are not available.

RESULTS

Selected distribution characteristics of NHL patients are listed in Table 1. The mean age at NHL diagnosis was *49.5* years (median, 50; range 28 to 69 y). Most patients presented with advanced disease, typically with low-grade follicular lymphomas. Subjects were followed-up for a mean of 9.7 years (median, 8.6; range, 2 to 21.7) after NHL diagnosis. Forty-eight, 27, and 12 patients were followed-up for 5, 10, and 15 years, respectively. By close of study, 44 patients had died, 16 remained alive, and one was lost to follow-up.

Subsequent courses of treatment included radiotherapy (12 patients), alkylating agents (six patients), or both (35 patients). Alkylating agent therapy typically consisted of cyclophosphamide-based regimens (25 patients) or chlorambucil (12 patients) with or without

Table 1. Selected Characteristics of NHL Patients

Characteristic	Men (n = 30)	Women (n = 31)	Total (N = 61)
Age at NHL diagnosis, years			
< 50	11	15	26
50-59	15	12	27
60-70	4	4	8
NHL stage			
I or II	5	6	11
III or IV	25	25	50
NHL classification*			
Low grade	22	25	47
Intermediate grade	2	1	3
High grade	2	2	4
Other or NOS	4	3	7
NHL pattern			
Follicular	18	21	39
Diffuse	7	7	14
Other	5	3	8†
NHL treatment (all)			
TBI only	4	4	8
TBI; subsequent RT	4	8	12‡
TBI; subsequent alkylating agents	4	2	6
TBI; subsequent RT and alkylating agents	18	17	35§
Subsequent solid tumors	4	4	8
Subsequent ANLL or MDS	5	0	5
Status at study end‖			
Alive	7	9	16
Dead	22	22	44
Lost to follow-up	1	0	1

Abbreviations: NOS, not otherwise specified; RT, radiotherapy.

*According to the Working Formulation classification system.[27]

†Includes 1 patient with follicular and diffuse patterns, and 7 for whom lymph node architecture could not be discerned from pathology reports.

‡Subsequent RT consisted of involved-field RT (11 patients) or a second course of TBI (1 patient). Of 11 patients who received involved-field RT, 2 later received high-dose TBI before bone marrow transplantation.

§Subsequent RT consisted of involved-field RT (31 patients), involved-field RT plus a second course of TBI (3 patients), or involved-field RT plus hemibody RT (1 patient). Of 31 patients who received involved-field RT alone, 2 later received high-dose TBI before bone marrow transplantation.

‖December 31, 1991.

Table 2. Cumulative Radiation Dose to ABM Among Patients With NHL

Treatment Group	No. of Patients	Dose (Gy) Median	Dose (Gy) Range	PY of Follow-Up After NHL dx	No. of ANLLs	No.,* Site, and Histology of Solid Tumors (latency after NHL dx, years)
TBI only	8	1.5	1.5-1.8	61	0	3: stomach, adenocarcinoma (3.6) kidney, renal cell carcinoma (6.5) thyroid, papillary carcinoma (6.8)
TBI; subsequent RT	12	5.8	1.5-16.7	168	0	0
TBI; subsequent alkylating agents	6	1.5	1.2-1.7	60	1	2: prostate, adenocarcinoma (3.3 and 12.7)
TBI; subsequent RT and alkylating agents	35	8.8	1.1-20.7	305	4	3: breast, adenocarcinoma (6.4) breast, unknown histology (9.3) colon, adenocarcinoma (13)
All patients	61	5.2	1.1-20.7	594	5	8

Abbreviation: dx, diagnosis.

*Number of patients in whom second cancers developed.

cyclophosphamide. Other cytotoxic drugs were given to four additional patients. Cyclophosphamide was typically administered with vincristine and prednisone (CVP)[30]; doxorubicin, vincristine, and prednisone (CHOP)"; vincristine, procarbazine, and prednisone (COPP)[32]; or bleomycin, doxorubicin, vincristine, and prednisone (BACOP).[33] The median duration of all subsequent chemotherapy was approximately 18 months (mean, 25.9; range, 1.7 to 97).

The median cumulative dose of radiation to ABM among all 61 patients was 5.2 Gy (range, 1.1 to 20.7 Gy) (Table 2). The dose varied according to administration of subsequent treatment. Among eight patients who received no therapy following TBI, the median dose to bone marrow was 1.5 Gy. The radiation dose to bone marrow (median, 8.8 Gy) was greatest among 35 subjects who later received combined modality treatment (CMT). Five ANLLs and eight solid tumors were subsequently identified among the NHL cohort.

Clinicopathologic data for patients who developed secondary ANLL are listed in Table 3. All patients who developed ANLL were men and all received salvage treatment, typically with both radiotherapy and alkylating agents (patients no. 1 to 3, and 5). Patient no. 1 underwent autologous bone marrow transplantation (ABMT) for recurrent NHL 9 years after initial diagnosis. ANLL occurred about 3 years after transplantation. Among all patients, treatment-related ANLL developed a median of 9.1 years after NHL diagnosis (range, 2.6 to 13.1). Survival after ANLL was poor (median, 6.5 months; range, 1 to 8).

All four leukemias could be considered excessive in comparison with the general population, since only 0.034 cases were expected (0/E, 117; 95% confidence interval, 31.5 to 300) (Table 4). There was no evidence of a relationship between leukemia and radiation dose to bone marrow, although analyses were limited by the small number of available ANLL cases.

For all solid tumors taken together, a nonsignificant twofold risk was apparent, with site-specific excesses listed in Table 4. Cumulative risk rates for ANLL and all second cancers were 17% and 37%, respectively, 15 years after NHL diagnosis (Fig 1).

DISCUSSION

Despite the small number of NHL patients studied, only 61, a significant excess of leukemic conditions developed in five (or 8%). This remarkable increase appeared related to the combination of TBI followed by salvage therapy that included alkylating agents. Within our series, the cumulative 15-year risk of leukemia was 17% and the relative risk (RR) was 117. In contrast, for acute radiation exposure situations, the cumulative risk of leukemia is less than 4%.[34] Large excesses of leukemia are never seen in populations exposed only to ionizing radiation, but they can be quite high following intense chemotherapeutic exposures. It thus is likely that subsequent chemotherapy contributed to the excess risk of leukemia in our series, either directly or by enhancing the effect of low-dose TBI. Data from animal studies suggest that low-dose TBI may expand the number of bone marrow stem cells subject to potential transformation by alkylating agents.[35] One multicenter investigation of breast cancer patients given large-field chest wall irradiation and chemotherapy suggested a multiplication of the individual risks from these two leukemogenic therapies.[36]

Our previous quantitative study of leukemia following NHL[23] showed an association with cytotoxic drugs, but RRs (range, twofold to 13-fold) were much lower than observed in the present series, although similar chemo-

Table 3. Secondary ANLL or MDS Following NHL: Clinicopathologic Data

	NHL						Secondary ANLL or MDS		
Patient No.	Age (years)*/Sex	NHL dx (month/year)	NHL Stage	Initial Therapy (RT dose to ABM, Gy)	Subsequent Therapy†	Total RT Dose (Gy) to ABM	Time Since NHL (years)	FAB dx	Survival After ANLL (months)
1	35/M	5/77	2	TBI (1.5)	CTX—6 months M-BACOD—6 cycles RT: left groin BMT: TBI, CTX—2 months	18.9	12.3	ANLL, NOS	3.7
2‡	47/M	3/78	4	TBI (1.5)	CHLB—7 months CTX—11 months RT: 2 courses¶	1.8#	13.1	MDS, RA	7.1
3	53/M	8/71	3	TBI (1.2)	TBI—2nd course RT: 2 courses§ CVP—2 cycles	4.1	2.6	ANLL, M6	6.5
4	52/M	1/72	3	TBI (1.4)	COPP—9 cycles CHLB—94 months	1.4	8.8	ANLL, NOS	8.0
5	55/M	7/73	3	TBI (1.5) RT, inverted-Y (5.8)	BACOP—2 cycles RT: 3 courses‖ CVP—23 cycles CTX—9 months	18.0	9.1	ANLL, NOS	1.0

Abbreviations: ADR, doxorubicin; BACOP, bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone; BMT, bone marrow transplantation; CHLB, chlorambucil; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; CTX, cyclophosphamide; CVP, cyclophosphamide, vincristine, and prednisone; CYTA, cytarabine; FAB, French-American-British; HBI, hemibody RT; M-BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; M, male; N/A, not available; RA, refractory anemia.

*Age at diagnosis of NHL.

†Therapy given before diagnosis of ANLL or MDS.

‡Since population cancer rates do not include MDS, this patient was excluded from calculations of O/E ratios and excess risks.

§Course 1 (given immediately after second TBI): right neck, both axillae. Course 2: left groin.

‖Course 1: head and neck, supraclavicular nodes, and right axilla. Course 2: left semi-mantle, abdomen, and pelvis. Course 3: whole brain.

¶Course 1: hemibody skin treatment. Course 2: lumbar spine (records insufficient to estimate dose).

#Represents minimum dose.

therapy regimens were used. Other types of NHL treatment that combine large-field radiotherapy with alkylating agents have also been associated with large risks (100- to 1,000-fold) of ANLL.[11,37] Results of these investigations[11,37] and other analytic series of ANLL following NHL[23,38-40] are listed in Table 5. Lower risks (twofold to 13-fold) of secondary ANLL have been noted in several prior reports,[39-41] with 76-fold excesses following

Table 4. Risk of Second Primary Cancer Following NHL

Site	Observed	Expected*	O/E	95% CI
All second cancers†	12	4.25	2.8	1.5-4.9
All solid tumors	8	3.97	2.0	0.9-4.0
Stomach	1	0.10	9.7	0.1-53.7
Rectum	1	0.22	4.6	0.1-25.7
Breast	2	0.56	3.6	0.4-12.9
Prostate	2	0.39	5.1	0.6-18.5
Kidney	1	0.11	9.0	0.1-50.0
Thyroid	1	0.03	34.5	0.5-192
ANLL†	4	0.03	117‡	31.5-300

Abbreviation: CI, confidence interval.

*Expected numbers have been rounded to 2 decimal places.

†Since population cancer rates do not include MDS, the patient with secondary MDS was excluded from calculations of O/E ratios and excess risks.

‡$P < .05$.

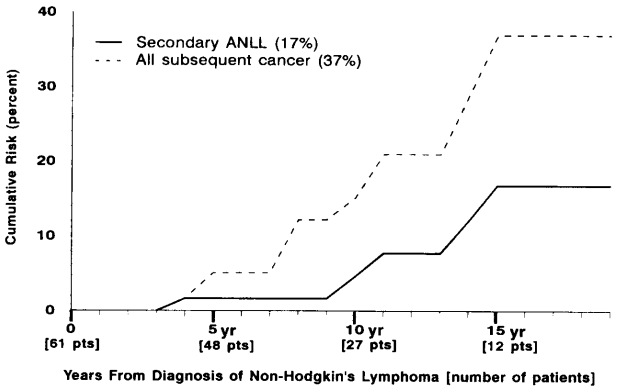

Fig 1. Cumulative risk of second primary cancers among 61 2-year survivors of NHL. Second cancers occurring < 2 years after NHL diagnosis are not included in the estimates. Percentages in parentheses indicate actuarial risk at 15 years.

Table 5. Overview of Analytic Studies of Secondary ANLL Following NHL

First Author, Year	No. of NHL Patients	Type of Treatment for NHL	No. of ANLLs	Risk (95% CI or *P* value)	
Gomez, 1982[37]	41	Total lymphoid irradiation	1	O/E	162 (n/a)
	40	Total lymphoid irradiation, carmustine, mechlorethamine, cyclophosphamide, vincristine	4	O/E	1,082 (n/a)
	81	All treatments	5	O/E	341 ($P < 0.001$)
Greene, 1983[11]	517	Varied: involved- or extended-field radiotherapy, TNR, TBI, or HBI, chemotherapy (frequently cyclophosphamide)	9	O/E	105 (48-199)
Pedersen-Bjergaard, 1985[38]	498	Alkylating agents, usually long-term cyclophosphamide	9	O/E	76 (n/a)
Lavey, 1990[39]	322	Chemotherapy	5	RR	10.6 (3.4-24.8)
	72	RT	0	RR	0 (0-183)
	292	CMT	4	RR	11.9 (3.2-30.6)
Lishner, 1991[40]	3,021	Varied: RT and/or chemotherapy	8	RR	6.9 (2.9-13.1)
Travis, 1994[23]*	11,386	Prednimustine	4	RR	13.4 (1.1-156)
		Mechlorethamine/procarbazine	4	RR	12.6 (2.0-79)
		Cyclophosphamide	11	RR	1.8 (0.7-4.9)
		Chlorambucil	6	RR	2.4 (0.7-8.6)
		RT, high-dose	6	RR	3.1 (0.7-13.7)

Abbreviations: n/a, not available; TNR, total-nodal irradiation.

*Case-control study: referent group for calculation of RRs associated with alkylating agents consisted of patients not given these drugs. Referent group for high-dose RT group (defined by median cumulative dose to bone marrow, or 6.35 Gy) consisted of patients who received no RT or low-dose RT (< 6.35 Gy).

denhall et al[12] did not include risk estimates (and thus is not listed in Table 5), four secondary myeloproliferative disorders occurred among 44 NHL patients given low-dose TBI as primary therapy. It is noteworthy that the overall proportions of NHL patients with secondary ANLL are similar in the present study and the survey reported by Mendenhall et al,[12] ie, 8% (five of 61) and 9% (four of 44), respectively.

Women constituted approximately 50% of our initial NHL cohort, but all secondary ANLLs occurred in men. This is an unusual finding, and may be due to chance, given the small numbers of patients in our study. Of analytic series in which patient sex is specified,[11,23,38,40] 44 men and 18 women developed secondary ANLL after NHL, but risk estimates were generally not stratified by sex. In our prior survey, excesses of ANLL following alkylating agent therapy were comparable among men and women.[23]

One of the NHL patients in our series developed secondary ANLL several years following ABMT. Estimates of the cumulative risk of secondary MDS/ANLL 5 to 6 years after ABMT for NHL range from 4% to 18%[3,42,43]; however, the roles of prior therapy and the preparative regimen for transplantation are difficult to distinguish.[3,42,43] Similar to our subject, most lymphoma patients tend to be intensively treated, even before ABMT.[42,43]

The twofold risk of solid tumors, although based on only eight cases, is noteworthy if large numbers of patients are ever treated with these combined modalities, eg, recipients of bone marrow transplants. The breast and thyroid are highly susceptible to carcinogenic induction by ionizing radiation; however, there is a strong modifying effect with age at exposure, with risk being lower with increasing age. Cancers at these sites can also be readily ascertained by intense screening, which might be afforded patients who return frequently to the c1inic for follow-up visits. Similarly, prostate cancer is also highly detectable in patient populations that undergo close surveillance.[44] Future studies are needed to determine the potential adverse effects among long-term survivors who received high-dose TBI and concomitant chemotherapy.

The optimal management of advanced-stage, low-grade NHL has not been defined.[12] Since many patients survive for prolonged periods without medical intervention,[45] effective therapeutic strategies that minimize adverse effects should be selected. Most patients with advanced-stage, low-grade NHL will eventually relapse, as in the present study, necessitating re-treatment, typically with alkylating agents. In choosing patient therapy, clinicians should be apprised of the large relative risk of ANLL associated with low-dose TBI followed by salvage therapy and balance this against survival benefit. Mendenhall et

al[12] suggest that low-dose TBI not be administered as primary treatment for NHL, in view of other available options.

Low-dose TBI, given alone[4] or with other therapeutic modalities,[7,8] has also been recently used as initial treatment for CLL and the management of nonneoplastic diseases refractory to other therapies .[9,10]) The efficacy of these treatment approaches should also be carefully considered in light of possible late effects and the availability of alternative therapies, particularly for CLL.[46]

Our results must be viewed in light of several strengths and limitations of the present investigation. Strong points include the careful definition of the study cohort, ascertainment of subsequent therapy, estimation of radiation dose to bone marrow, and histologic confirmation of diagnoses. The small number of patients available for study remains the most serious limitation. Nonetheless, our results suggest that low-dose TBI followed by salvage therapy is associated with a risk of ANLL that may greatly supersede those following some NHL treatments,[23,39-41] but not others.[11,37,38] The exceptional disparity between the leukemogenicity of NHL treatments in our prior study[23] and those in the current report is also evident when excess risks are compared. Approximately six excess ANLLs might be expected to occur among 10,000 NHL patients treated with selected regimens that include low cumulative doses of cyclophosphamide and monitored for 15 years.[23] Therapy with prednimustine might yield 93 excess ANLLs over the same period,[23] whereas primary management with TBI followed by salvage treatment could result in 869 excess ANLLs.

Follow-up data of other patients treated with low-dose TBI[3-8,11,13-21] would be informative to confirm the high risk of subsequent ANLL reported here and suggested by the data of Mendenhall et al.[12] Cytogenetic and molecular studies of ANLL that occurs in this unusual setting may also provide further insights into underlying mechanisms of leukemogenesis. The risk of solid tumors following TBI, either low-dose or high-dose, is also not well defined, and might become an important consideration for patients, especially children, who survive for long periods after bone marrow transplantation.

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